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Patent- og Varemærkestyrelsen
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PATENT- G VAREMÆRKESTYRELSEN

PHARMACEUTICAL USE OF BORONIC ACIDS AND ESTERS THEREOF

FIELD OF THE INVENTION

The present invention relates to use of compounds and pharmaceutical compositions containing them for treating medical disorders where it is desirable to modulate the activity of hormone-sensitive lipase

BACKGROUND OF THE INVENTION

The overall energy homeostasis of a mammalian system requires a high degree of regulation to ensure the availability of the appropriate substrate at the appropriate time Plasma glucose levels rise during the post-prandial state, to return to pre-prandial levels within 2-3 hours During these 2-3 hours, insulin promotes glucose uptake by skeletal muscle and adipose tissue and decreases the release of free fatty acids (FFA) from adipocytes, to ensure that the two substrates do not compete with each other When plasma glucose levels fall, an elevation in plasma FFA is necessary to switch from glucose to fat utilization by the various tissues

In individuals with insulin resistance, FFA levels do not fall in response to insulin, as they do in normal individuals, preventing the normal utilization of glucose by skeletal muscle, adipose and liver Furthermore, there is a negative correlation between insulin sensitivity and plasma FFA levels

Hormone-sensitive lipase (HSL) is an enzyme, expressed primarily in adipocytes but also in adrenal gland, pancreatic β-cells, macrophages and testicles HSL catalyses the hydrolysis of triglycerides to diglycerides and the subsequent hydrolysis of diglycerides and, to some extent, monoglycerides (Frederikson et al , 1981) It is through the regulation of this nzyme that the levels of circulating FFA are modulated Insulin leads to the inactivation of HSL with a subsequent fall in plasma FFA levels during the post-prandial state, followed by the activation of the enzyme when the insulin concentration falls and catecholamines rise during the post-absorptive period The activation of HSL l ads to an increase in plasma FFA, as they become the main source of energy during fasting

The activation-inactivation of HSL is primarily mediated through the cAMP-protein kinase A and AMP-dependent kinase pathways There are compounds like nicotinic acid and its derivatives, that decrease the activation of HSL via these pathways and cause a decrease in lipolysis that leads to a reduction in the FFA levels These drugs have a beneficial effect in the utilization of glucose and in the normalization of the excess triglyceride synthesis seen in patients with elevated FFA However, since these pathways are used by other processes in the body, these drugs have severe side effects

Boronic acids and derivatives thereof have been shown to have a number of enzyme-inhibitory properties Certain boronic acids have been shown to inhibit beta-lactamases and have antibacterial applications when combined with beta-lactam antibiotics (US 6,075,014) WO 98/31688 discloses boronic acid derivatives claimed useful as angiogenesis inhibitors FR 2,758,329 discloses (4(5-imidazolyl(butyl) boronic acid derivatives containing a 1,2-dihydro-2-oxo-1-pyridinyl group, and their antithrombotic activity EP 792883 discloses boronic acid derivative with are thrombin-inhibiting and trypsin-like serine protease-inhibiting However, these references neither disclose nor suggest that boronic acids or derivatives thereof may have HSL inhibitory activity

We have found boronic acids and esters thereof that specifically inhibit the lipolytic activity of HSL and lead to a decrease in plasma FFA levels These compounds can be used to treat disorders where a decreased level of plasma FFA is desired, such as insulin resistance, syndrome X, dyslipidemia, abnormalities of lipoprotein metabolism

One object of the present invention is to provide compounds and pharmaceutical compositions that inhibit the lipolytic activity of HSL A further object is to provide compounds which have good pharmaceutical properties such as solubility, bioavailability etc

DEFINITIONS

The following is a detailed definition of the terms used to describe the compounds of the invention

"Halogen" designates an atom selected from the group consisting of F, Cl, Br and I

The term "C_{1-6}-alkyl" in the present context designates a saturated, branched or straight hydrocarbon group having from 1 to 6 carbon atoms Representative examples include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl, n-pentyl, isopentyl, neopentyl, *tert*-pentyl, n-hexyl, isohexyl and the like

The term "C_{2-6}-alkyl" in the present context designates a saturated, branched or straight hydrocarbon group having from 2 to 6 carbon atoms Representative examples include, but are not limited to, ethyl, n-propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl, n-pentyl, isopentyl, neopentyl, *tert*-pentyl, n-hexyl, isohexyl and the like

The term "C_{1-6}-alkoxy" in the present context designates a group –O-C_{1-6}-alkyl wherein C_{1-6}-alkyl is as defined above Representative examples include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, butoxy, isobutoxy, *sec*-butoxy, *tert*-butoxy, n-pentoxy, isopentoxy, neopentoxy, *tert*-pentoxy, n-hexoxy, isohexoxy and the like

The term "C_{1-6}-alkylthio" in the present context designates a group –S-C_{1-6}-alkyl wherein C_{1-6}-alkyl is as defined above Representative examples include, but are not limited to, methylthio, ethylthio, isopropylthio, n-propylthio, t-butylthio, n-pentylthio and the like

The term "C_{2-6}-alkenyl" as used herein, represent an olefinically unsaturated branched or straight hydrocarbon group having from 2 to 6 carbon atoms and at least on double bond Examples of such groups include, but are not limited to, vinyl, 1-propenyl, 2-propenyl, allyl, iso-propenyl, 1,3-butadienyl, 1-butenyl, hexenyl, pentenyl and the like

The term "C_{2-6}-alkynyl" as used herein, represent an unsaturated branched or straight hydrocarbon group having from 2 to the specified number of carbon atoms and at least one triple bond Examples of such groups include, but are not limited to, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, 2-pentynyl and the like

The term "C_{3-10}-cycloalkyl" as used herein represents a saturated mono-, bi-, tri- or spirocarbocyclic group having from 3 to 10 carbon atoms Representative examples are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, bicyclo[3 2 1]octyl, spiro[4 5]decyl, norpinyl, norbonyl, norcaryl, adamantyl and the like

The term "C_{3-8}-heterocyclyl" as used herein represents a saturated 3 to 8 membered ring containing one or more heteroatoms selected from nitrogen, oxygen and sulfur Representative examples are pyrrolidyl, piperidyl, piperazinyl, morpholinyl, thiomorpholinyl, aziridinyl, tetrahydrofuranyl and the like

The term "aryl" as used herein represents a carbocyclic aromatic ring system being either monocyclic, bicyclic, or polycyclic, such as phenyl, biphenyl, naphthyl, anthracenyl, phenanthrenyl, fluorenyl, indenyl, pentalenyl, azulenyl, biphenylenyl and the like Aryl is also intended to include the partially hydrogenated derivatives of the carbocyclic aromatic systems enumerated above Non-limiting examples of such partially hydrogenated derivatives are 1,2,3,4-tetrahydronaphthyl, 1,4-dihydronaphthyl and the like

The term "aryloxy" as used herein represents an aryl which is linked via an oxygen atom, e g phenoxy, 1-naphthyloxy, 2-naphthyloxy and the like

The term "heteroaryl" as used herein represents a heterocyclic aromatic ring system containing one or more heteroatoms selected from nitrogen, oxygen and sulfur such as furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5- triazinyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, tetrazolyl, thiadiazinyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl (thianaphthenyl), indazolyl, benzimidazolyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, purinyl, quinazolinyl, quinolizinyl, quinolinyl, isoquinolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, azepinyl, diazepinyl, acridinyl and the like Heteroaryl is also intended to include the partially hydrogenated derivatives of the heterocyclic systems enumerated above Non-limiting examples of such partially hydrogenated derivatives are 2,3-dihydrobenzofuranyl, 3,4-dihydroisoquinolinyl, pyrrolinyl, pyrazolinyl, indolinyl, oxazolidinyl, oxazolinyl, oxazepinyl and the like

The term "heterocyclic system" as used herein includes aromatic as well as non-aromatic ring moieties, which may be monocyclic, bicyclic or polycyclic, and containing in their ring structure one or more heteroatoms selected from nitrogen, oxygen and sulfur Non-limiting examples of such heterocyclic systems are C_{3-8}-heterocyclyl and heteroaryl

Certain of the above defined terms may occur more than once in the structural formulae, and upon such occurrence each term shall be defined independently of the other

The term "optionally substituted" as used herein means that the groups in question are either unsubstituted or substituted with one or more of the substituents specified When the groups in question are substituted with more than one substituent the substituents may be the same or different

The term "optionally covalently bound" as used herein means that the substituents in question are either not covalently bound to each other or the substituents are directly connected to each other by a covalent bond A non-limiting example of such optionally covalently bound substituents is -N-ethyl-n-propyl which provided that the substituents, ethyl and n-propyl, are optionally covalently bound may be –N-ethyl-n-propyl, 1-piperidyl, 3-methyl-1-pyrrolidyl or 2,3-dimethyl-1-azetidyl

DETAILED DESCRIPTION OF THE INVENTION

One aspect of the present invention is the use of a boronic acid, an ester thereof, a prodrug thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof for

a) inhibition of the lipolytic activity of hormone-sensitive lipase against triacylglycerols, diacylglycerols, cholesterol acyl esters or steroid acyl esters, and/or

b) modulating the plasma level of free fatty acids, glycerol, LDL-cholesterol, HDL-cholesterol, insulin and/or glucose, and/or

c) modulating intracellular triacylglycerol and cholesterol ester stores, intracellular level of fatty acids, fatty acid esters such as diacylglycerols, phosphatidic acids, long chain acyl-CoA´s as well as citrate or malonyl-CoA, and/or

d) increasing insulin sensitivity in adipose tissue, skeletal muscle, liver or pancreatic β cells, and/or

e) modulating insulin secretion from pancreatic β cells, and/or

f) inhibition of male fertility

in a patient

In this application the term "treatment" is defined as the management and care of a patient for the purpose of combating or alleviating the disease, condition or disorder, and the term includes the administration of the active compound to prevent the onset of the symptoms or complications, or alleviating the symptoms or complications, or eliminating the disease, condition, or disorder

In this application the term "pharmaceutically acceptable" is defined as being suitable for administration to humans without adverse events

In this application the term "prodrug" is defined as a chemically modified form of the active drug, said prodrug being administered to the patient and subsequently being converted to the active drug Techniques for development of prodrugs are well known in the art

A second aspect of the present invention is the use of a boronic acid, an ester thereof, a prodrug thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof for the preparation of a medicament for the treatment of any disorder where it is desirable to

a) inhibit the lipolytic activity of hormone-sensitive lipase against triacylglycerols, diacylglycerols, cholesterol acyl esters or steroid acyl esters, and/or

b) modulate the plasma level of free fatty acids, glycerol, LDL-cholesterol, HDL-cholesterol, insulin and/or glucose, and/or

c) modulate intracellular triacylglycerol and cholesterol ester stores, intracellular level of fatty acids, fatty acid esters such as diacylglycerols, phosphatidic acids, long chain acyl-CoA´s as well as citrate or malonyl-CoA, and/or

d) increase insulin sensitivity in adipose tissue, skeletal muscle, liver or pancreatic β cells, and/or

e) modulate insulin secretion from pancreatic β cells, and/or

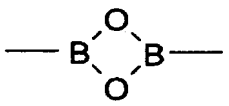
f) inhibit male fertility

in a patient

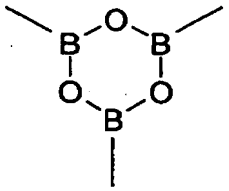
In one embodiment pK_a of said boronic acid, an ester thereof, a prodrug thereof or a pharmaceutically acceptable salt thereof is between 2 0 and 11 5, between 3 0 and 10 5, between 4 0 and 9 5, between 5 0 and 8 5, preferably between 5 5 to 8 0, and most preferable between 6 0 to 7 5

In another embodiment the boronic acid, an ester thereof or a prodrug thereof is a dimer or trimer of a boronic acid

In a further embodiment said dimer or trimer of a boronic acid comprises a structure selected from

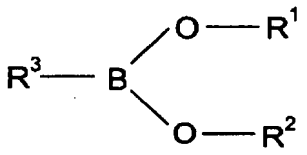


and



In another embodiment said boronic acid, an ester thereof or a prodrug thereof comprises an atom selected from the group consisting of S, P, I, Br, Si, Se and Ge

In another embodiment said boronic acid, an ester thereof or a prodrug thereof is of the general formula I



(I)

wherein R^1 and R^2 are independently selected from hydrogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfonyl, sulfinyl, amino, imino, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, $C_{2\,6}$-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfonyl, sulfinyl, amino, imino, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfonyl, sulfinyl, amino, imino, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, het roaryl, C_{3-8}-

heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfonyl, sulfinyl, amino, imino, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl,

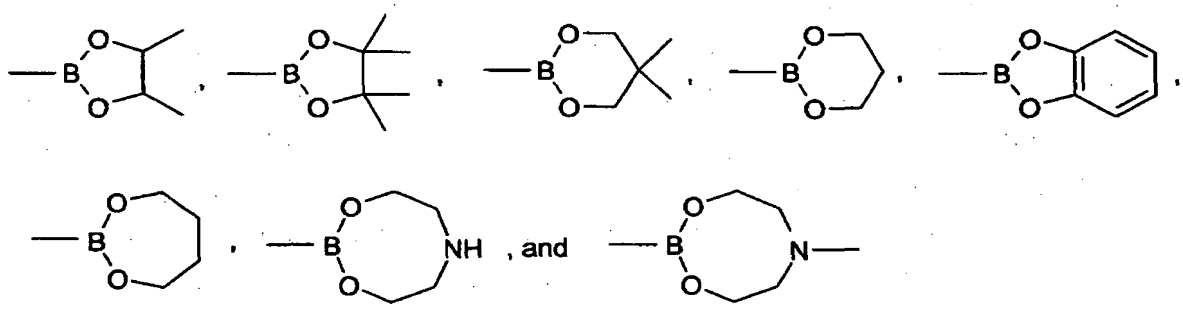
wherein R^2 is optionally covalently bound to R^1 by one or two ether, thioether, O-B, C-C, C=C or C-N bonds, to form a ring system with the O-atoms to which R^1 and R^2 are bound, and

R^3 is selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfonyl, sulfinyl, amino, imino, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfonyl, sulfinyl, amino, imino, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfonyl, sulfinyl, amino, imino, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfonyl, sulfinyl, amino, imino, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, h teroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally sub-

stituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfonyl, sulfinyl, amino, imino, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl,

or any tautomeric forms, stereoisomers, mixture of stereoisomers including a racemic mixture, oligomers or polymorphs

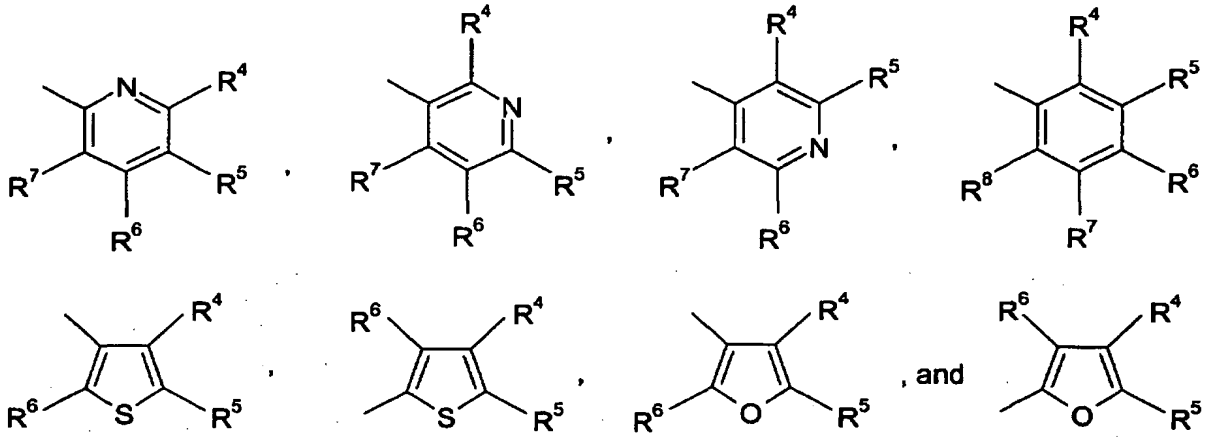
In another embodiment said boronic acid, an ester thereof, or a prodrug thereof, comprises a structure selected from the group consisting of



In another embodiment the group R^3 in the general formula (I) comprises an optionally substituted moiety selected from the group consisting of pyrrolidine-2-yl, pyrrolidine-3-yl, pyrrole-2-yl, pyrrole-3-yl, 3H-pyrrole-2-yl, 3H-pyrrole-3-yl, 3H-pyrrole-4-yl, 3H-pyrrole-5-yl, oxolane-2-yl, oxolane-3-yl, furane-2-yl, furane-3-yl, thiolane-2-yl, thiolane-3-yl, thiophene-2-yl, thiophene-3-yl, pyrazole-3-yl, pyrazole-4-yl, pyrazole-5-yl, pyrazolidine-3-yl, pyrazolidine-4-yl, imidazole-2-yl, imidazole-4-yl, imidazole-5-yl, imidazolidine-2-yl, imidazolidine-4-yl, 3H-pyrazole-3-yl, 3H-pyrazole-4-yl, 3H-pyrazole-5-yl, isoxazole-3-yl, isoxazole-4-yl, isoxazole-5-yl, oxazole-2-yl, oxazole-4-yl, oxazole-5-yl, isothiazole-3-yl, isothiazole-4-yl, isothiazole-5-yl, thiazole-2-yl, thiazole-4-yl, thiazole-5-yl, 1,2,5-oxadiazole-3-yl, 1,3,5-oxadiazole-2-yl, 1,3,5-oxadiazole-4-yl, 1,3,4-oxadiazole-2-yl, 1,2,3,5-oxatriazole-4-yl, 1,2,5-thiadiazole-3-yl, 1,3,5-thiadiazole-2-yl, 1,3,5-thiadiazole-4-yl, 1,3,4-thiadiazole-2-yl, 1,2,3,5-thiatriazole-4-yl, 1,2,3-triazole-4-yl, 1,2,3-triazole-5-yl, 1,2,4-triazole-3-yl, 1,2,4-triazole-5-yl, 1,2,5-triazole-3-yl,

tetrazole-5-yl, 1,3-oxathiole-2-yl, 1,3-oxathiole-4-yl, 1,3-oxathiole-5-yl, benzofurane-2-yl, benzofurane-3-yl, isobenzofurane-1-yl, benzothiophene-2-yl, benzothiophene-3-yl, isobenzothiophene-1-yl, 1H-indole-2-yl, 1H-indole-3-yl, 2H-isoindole-1-yl, indolizine-1-yl, indolizine-2-yl, indolizine-3-yl, 1H-benzimidazole-2-yl, 1H-benzothiazole-2-yl, 1H-benzoxazole-2-yl, 1H-benzisooxazole-3-yl, 3H-indazole-3-yl, piperedine-1-yl, piperedine-2-yl, piperedine-3-yl, piperedine-4-yl, piperazine-1-yl, piperazine-2-yl, 2,5-dione-piparazine-1-yl, 2,5-dione-piparazine-3-yl and phenyl

In another embodiment the group R^3 is selected from the group consisting of



wherein R^4, R^5, R^6, R^7 and R^8 are independently selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfonyl, sulfinyl, amino, imino, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfonyl, sulfinyl, amino, imino, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl,

heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfonyl, sulfinyl, amino, imino, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfonyl, sulfinyl, amino, imino, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl

In another embodiment the molar weight of each of R^4, R^5, R^6, R^7 and R^8 are below about 100 Dalton, preferably below about 80 Dalton, more preferable below 50 Dalton and even more preferable below about 20 Dalton

In another embodiment R^4, R^5, R^6, R^7 and R^8 are independently selected from hydrogen, halogen, hydroxyl, perhalomethyl, perhalomethoxy, C_{1-6}-alkyl, C_{1-6}-alkoxy and C_{1-6}-alkylthio

In another embodiment R^4, R^5, R^6, R^7 and R^8 are independently selected from hydrogen, halogen, methyl, methoxy, thiomethoxy, perhalomethyl, perhalomethoxy

In another embodiment R^4, R^5, R^6, R^7 and R^8 are independently selected from hydrogen, halogen, trifluoromethyl and trifluoromethoxy

In another embodiment the group R^1 is H

In another embodiment the group R^1 is H and the group R^2 is H

In another embodiment said boronic acid, an ester thereof or a prodrug thereof is selected from the group consisting of

2-(5-Chlorothiophen-2-yl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane,

2-(5-Chlorothiophen-2-yl)-5,5-dimethyl-[1,3,2]dioxaborinane,

2-(5-Chlorothiophen-2-yl)-[1,3,6,2]dioxazaborocane,

2-(3,5-Difluorophenyl)-[1,3,6,2]dioxazaborocane,
2-(3-Bromophenyl)-[1,3,6,2]dioxazaborocane,
2-(3-Chlorophenyl)-[1,3,6,2]dioxazaborocane,
2-(3-Fluorophenyl)-[1,3,6,2]dioxazaborocane,
2-(3-Trifluoromethylphenyl)-[1,3,6,2]dioxazaborocane,
2-(3,4,5-Trifluorophenyl)-[1,3,6,2]dioxazaborocane,
2-(3-Chlorophenyl)-5,5-dimethyl-[1,3,2]dioxaborinane,
5,5-Dimethyl-2-(3-trifluoromethylphenyl)-[1,3,2]dioxaborinane,
2-(5-Chloro-2-methoxyphenyl)-[1,3,6,2]dioxazaborocane,
2-(3-Trifluoromethoxyphenyl)-[1,3,6,2]dioxazaborocane,
2-(3,5-Dichlorophenyl)-[1,3,6,2]dioxazaborocane,
2-(3-Chloro-4-fluorophenyl)-[1,3,6,2]dioxazaborocane,
2-(4-Methylthiophen-2-yl)-[1,3,6,2]dioxazaborocane,
2-(3-Bromophenyl)-5,5-dimethyl-[1,3,2]dioxaborinane,
2-(5-Chloro-2-methoxyphenyl)-5,5-dimethyl-[1,3,2]dioxaborinane,
5,5-Dimethyl-2-(3,4,5-trifluorophenyl)-[1,3,2]dioxaborinane,
5,5-Dimethyl-2-(3-trifluoromethoxyphenyl)-[1,3,2]dioxaborinane,
2-(3,5-Dichlorophenyl)-5,5-dimethyl-[1,3,2]dioxaborinane,
2-(3-Chloro-4-fluorophenyl)-5,5-dimethyl-[1,3,2]dioxaborinane,
2-(3-Fluorophenyl)-5,5-dimethyl-[1,3,2]dioxaborinane,
5,5-Dimethyl-2-(4-methylthiophen-2-yl)-[1,3,2]dioxaborinane,
2-(3-Bromophenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane,
2-(5-Chloro-2-methoxyphenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane,
4,4,5,5-Tetramethyl-2-(3-trifluoromethoxyphenyl)-[1,3,2]dioxaborolane,
2-(3,5-Dichlorophenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane,
2-(3-Chloro-4-fluorophenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane,
2-(3-Chlorophenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane,
4,4,5,5-Tetramethyl-2-(3-trifluoromethylphenyl)-[1,3,2]dioxaborolane,
4,4,5,5-Tetramethyl-2-(4-methylthiophen-2-yl)-[1,3,2]dioxaborolane,
4-Benzyloxyphenylboronic acid,
4-BROMOBENZENEBORONIC ACID N-METHYLDIETHANOLAMINE CYCLIC ESTER,
2-(3,5-DIFLUOROPHENYL)-5,5-DIMETHYL-1,3,2-DIOXABORINANE,3-BROMOBENZENEBORONIC ACID N-METHYLDIETHANOLAMINE CYCLIC ESTER,
2-(4-BROMOPHENYL)-5,5-DIMETHYL-1,3,2-DIOXABORINANE,
2-(2-chloroPHENYL)-5,5-DIMETHYL-1,3,2-DIOXABORINANE,

2-(5,5-Dimethyl-[1,3,2]dioxaborinan-2-yl)-benzonitrile,
2-(2-Fluoro-phenyl)-5,5-dimethyl-[1,3,2]dioxaborinane,
2-(5,5-Dimethyl-[1,3,2]dioxaborinan-2-yl)-benzoic acid ethyl ester,
5-CHLORO-2-METHOXYPHENYLBORONIC ACID,
3,5-Dibromophenylboronic acid,
3-Ethoxyphenylboronic acid,
3-phenylphenylboronic acid,
4-fluorophenylboronic acid,
2-Bromophenylboronic acid,
3-Bromophenylboronic acid,
2,6-Dichlorophenylboronic acid,
3-Methylphenylboronic acid,
2-Chlorophenylboronic acid,
3-Chlorophenylboronic acid,
3-(TRIFLUOROMETHOXY)BENZENEBORONIC ACID,
3-Trifluoromethylphenylboronic acid,
3,5-Bis(Trifluoromethyl)phenylboronic acid,
3,5-Dichlorophenylboronic acid,
3-Chloro-4-fluorophenylboronic acid,
3,5-Difluorophenylboronic acid,
3-Fluorophenylboronic acid,
2,3-DIFLUORO-4-PENTYLPHENYLBORONIC ACID,
(3-FLUORO-4-BENZYLOXYPHENYL)BORONIC ACID,
3,4,5-Trifluorophenylboronic acid,
2,3,5-Trichlorophenylboronic acid,
2,5-Dichlorophenylboronic acid,
2,3-Difluorophenylboronic acid,
2,5-Difluorophenylboronic acid,
4'-(4,4,5,5-TETRAMETHYL-1,3,2-DIOXABOROLAN-2-YL)ACETANILIDE,
3,4-Difluorophenylboronic acid,
2,3-Dichlorophenylboronic acid,
2,3-Difluoro-4-bromophenylboronic acid,
3-Fluoro-4-phenylboronic acid,
2-Methoxy5-fluorophenylboronic acid,
3,4-Dichlorophenylboronic acid,

5-INDOLYL BORONIC ACID,
3-Formylphenylboronic acid,
4-(N,N-DIMETHYLCARBAMOYL)PHENYLBORONIC ACID,
6-Methoxy-2-phenyl-hexahydro-pyrano[3,2-a][1,3,2]dioxaborinine-7,8-diol,
2-Fluoro-4-(5-pentyl-[1,3,2]dioxaborinan-2-yl)-benzoic acid,
4-(3-Iodo-phenoxymethyl)-2-phenyl-[1,3,2]dioxaborolane,
3'-(4,4,5,5-TETRAMETHYL-1,3,2-DIOXABOROLAN-2-YL)-2-trimethylsilylthiophen,
4'-(4,4,5,5-TETRAMETHYL-1,3,2-DIOXABOROLAN-2-YL)2-nitrothiophene,
1-BENZOTHIOPHEN-3-YLBORONIC ACID,
2-FORMYL-3-THIOPHENEBORONIC ACID,
2-THIEN-3-YL-1,3,2-BENZODIOXABOROLE,
3-Thiophenboronic acid,
2-(2-FORMYL-3-METHYLTHIEN-5-YL)-1,3,2-DIOXABORINANE,
4-METHYLTHIOPHENE-2-BORONIC ACID,
5-METHYLFURAN-2-BORONIC ACID,
5-Methylthiophene-2-boronic acid,
BENZO[B]FURAN-2-BORONIC ACID,Benzo[B]thiophene-2-boronic acid,Furan-2-boronic acid,5-Chlorothiophene-2-boronic acid,5-Cyanothiophene-2-boronic acid,5-Acetylthiophene-2-boronic acid,Thiophene-2-boronic acid,3-Bromothiophene-2-boronic acid and5,5-Dimethyl-2-(3-iodothiophen-2-yl)-[1,3,2]dioxaborinane

In another embodiment R^3 is characterized in pK_a of the compound R^3-$B(OH)_2$ being between 2 0 and 11 5, between 3 0 and 10 5, between 4 0 and 9 5, between 5 0 and 8 5, preferably between 5 5 to 8 0, and most preferable between 6 0 to 7 5

In another embodiment said boronic acid, an ester thereof or a prodrug thereof has a molar weight of no greater than 1000 D

In another embodiment the molar weight of said boronic acid, an ester thereof or a prodrug thereof is less than 750 D, preferably less than 500 D, more preferable less than 350 D, more preferable less than 300 D, more preferable less than 250 D and even more preferable less than 200 D

In another embodiment said boronic acid, an ester thereof or a prodrug thereof has an IC_{50} value as determin d by the assay 3190 2 or 3180 1 disclosed herein of less than 50

μM, preferably less than 5 μM, more preferable less than 500 nM and even more preferable less than 100 nM

In another embodiment said boronic acid, an ester thereof or a prodrug thereof has a solubility in water at 25 °C and pH 2 0 of at least 0 5 mg/L, preferably at least 2 5 mg/L, more preferable at least 20 mg/L, even more preferable at least 200 mg/L and most preferable at least 2 g/L

In another embodiment the administration of said boronic acid, an ester thereof or a prodrug thereof is by the oral, nasal, transdermal, pulmonal, or parenteral route

A third aspect of the invention concerns a pharmaceutical composition for the use according to the first and second aspects of the invention, wherein said pharmaceutical composition comprises, as an active ingredient, a boronic acid, an ester thereof, a prodrug thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, together with a pharmaceutically acceptable carrier or diluent

In one embodiment the pharmaceutical composition for the use according to the first and second aspects of the invention, wherein said pharmaceutical composition compris s, as an active ingredient, a boronic acid, an ester thereof or a prodrug thereof as defined in any of the above embodiments, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent

In another embodiment the pharmaceutical composition is in unit dosage form, comprising from about 0 05 mg to about 2000 mg, preferably from about 0 1 to about 500 mg of the boronic acid, an ester thereof, a prodrug thereof or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof as defined in any one of the above embodiments

In another embodiment the pharmaceutical composition is for oral, nasal, transdermal, pulmonal or parenteral administration

In a fourth aspect the invention concerns a method of treating any disorder where it is desirable to inhibit the lipolytic activity of hormone-sensitive lipase against triacylglycerols,

diacylglycerols, cholesterol acyl esters or steroid acyl esters, wherein said method comprises the use according to any on of the first, second or third aspects of the invention

In a fifth aspect the invention concerns a method of treating any disorder where it is desirable to modulate the plasma level of free fatty acids or to modulate the handling, storage and oxidation of intracellular fatty acid and cholesterol, wherein said method comprises the use according to any one of the first, second or third aspects of the invention

In one embodiment of the fourth and fifth aspects, said disorder is selected from the group consisting of insulin resistance, diabetes type 1, diabetes type 2, metabolic syndrome X, impaired glucose tolerance, hyperglycemia, dyslipidemia, obesity, abnormalities of lipoprotein metabolism and any combination thereof

In another aspect the invention concerns a method for the treatment of a patient suffering from insulin resistance, diabetes type 1, diabetes type 2, metabolic syndrome X, impaired glucose tolerance, hyperglycemia, dyslipidemia, hyperlipoproteinemia, hypertriglyceridemia, hyperlipidemia, hypercholesterolemia, or other abnormalities of lipoprotein metabolism, said method comprising administering to the patient a pharmaceutically effective amount of a boronic acid, an ester thereof, a prodrug thereof or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof

In one embodiment said boronic acid or an ester thereof, or a prodrug thereof is a compound according to any one of the first, second or third aspects of the invention

In another embodiment the patient is treated with said boronic acid, an ester thereof, a prodrug thereof or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof for at least about 1 week, for at least about 2 weeks, for at least about 4 weeks, for at least about 2 months or for at least about 4 months

The present invention also encompasses pharmaceutically acceptable salts of the present compounds Such salts include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable base addition salts, pharmaceutically acceptable metal salts, ammonium and alkylated ammonium salts Acid addition salts include salts of inorganic acids as well as organic acids Repres ntative examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, nitric acids and the like Representative

examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, lactic, maleic, malic, malonic, mandelic, oxalic, picric, pyruvic, salicylic, succinic, methanesulfonic, ethanesulfonic, tartaric, ascorbic, pamoic, bismethylene salicylic, ethanedisulfonic, gluconic, citraconic, aspartic, stearic, palmitic, EDTA, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, p-toluenesulfonic acids, sulphates, nitrates, phosphates, perchlorates, borates, acetates, benzoates, hydroxynaphthoates, glycerophosphates, ketoglutarates and the like Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in J Pharm Sci 1977, 66, 2, which is incorporated herein by reference Examples of metal salts include lithium, sodium, potassium, magnesium, zinc, calcium salts and the like Examples of amines and organic amines include ammonium, methylamine, dimethylamine, trimethylamine, ethylamine, diethylamine, propylamine, butylamine, tetramethylamine, ethanolamine, diethanolamine, triethanolamine, meglumine, ethylenediamine, choline, N,N'-dibenzylethylenediamine, N-benzylphenylethylamine, N-methyl-D-glucamine, guanidine and the like Examples of cationic amino acids include lysine, arginine, histidine and the like

The pharmaceutically acceptable salts are prepared by reacting the compound of formula I with 1 to 4 equivalents of a base such as sodium hydroxide, sodium methoxide, sodium hydride, potassium t-butoxide, calcium hydroxide, magnesium hydroxide and the like, in solvents like ether, THF, methanol, t-butanol, dioxane, isopropanol, ethanol etc Mixture of solvents may be used Organic bases like lysine, arginine, diethanolamine, choline, guandine and their derivatives etc may also be used Alternatively, acid addition salts wherever applicable are prepared by treatment with acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, p-toluenesulphonic acid, methanesulfonic acid, acetic acid, citric acid, maleic acid salicylic acid, hydroxynaphthoic acid, ascorbic acid, palmitic acid, succinic acid, benzoic acid, benzenesulfonic acid, tartaric acid and the like in solvents like ethyl acetate, ether, alcohols, acetone, THF, dioxane etc Mixture of solvents may also be used

The stereoisomers of the compounds forming part of this invention may be prepared by using reactants in their single enantiomeric form in the process wherever possible or by conducting the reaction in the presence of reagents or catalysts in their single enantiomer form or by resolving the mixture of stereoisomers by conventional methods Some of the preferred methods include use of microbial resolution, enzymatic resolution, resolving the diaster omeric salts formed with chiral acids such as mandelic acid, camphorsulfonic acid, tartaric acid, lactic acid, and the like wherever applicable or chiral bases such as brucine,

(*R*)- or (*S*)-phenylethylamine, cinchona alkaloids and their derivatives and the like Commonly used methods are compiled by Jaques et al in "Enantiomers, Racemates and Resolution" (Wiley Interscience, 1981) More specifically the compound of formula I may be converted to a 1 1 mixture of diastereomeric amides by treating with chiral amines, aminoacids, aminoalcohols derived from aminoacids, conventional reaction conditions may be employed to convert acid into an amide, the dia-stereomers may be separated either by fractional crystallization or chromatography and the stereoisomers of compound of formula I may be prepared by hydrolysing the pure diastereomeric amide

Various polymorphs of compound of general formula I forming part of this invention may be prepared by crystallization of compound of formula I under different conditions For example, using different solvents commonly used or their mixtures for recrystallization, crystallizations at different temperatures, various modes of cooling, ranging from very fast to very slow cooling during crystallizations Polymorphs may also be obtained by heating or melting the compound followed by gradual or fast cooling The presence of polymorphs may be determined by solid probe nmr spectroscopy, ir spectroscopy, differential scanning calorimetry, powder X-ray diffraction or such other techniques

The invention also encompasses prodrugs of the present compounds, which on administration undergo chemical conversion by metabolic processes before becoming active pharmacological substances In general, such prodrugs will be functional derivatives of the present compounds, which are readily convertible in vivo into the required compound of the formula (I) Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed H Bundgaard, Elsevier, 1985

The invention also encompasses active metabolites of the present compounds

The invention also relates to pharmaceutical compositions comprising, as an active ingredient, at least one compound of the formula I or any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof together with one or more pharmaceutically acceptable carriers or diluents

Furthermore, the invention relates to the use of compounds of the general formula I or their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts or pharmaceutically acceptable solvates thereof for the preparation of a pharmaceutical composition for the treatment and/or prevention of disorders where a decreased level of plasma FFA is desirable, such as the conditions mentioned above

In another aspect, the present invention relates to a method of treating and/or preventing type 2 diabetes, insulin resistance, metabolic syndrome X, impaired glucose tolerance, dyslipidemia and abnormalities of lipoprotein metabolism

In a still further aspect, the present invention relates to the use of one or more compounds of the general formulae I-XXXXII, or pharmaceutically acceptable salts thereof, for the preparation of a pharmaceutical composition for the treatment and/or prevention of type 2 diabetes, insulin resistance, metabolic syndrome X, impaired glucose tolerance, dyslipidemia and abnormalities of lipoprotein metabolism

In a still further aspect, the present compounds are useful for the delaying or prevention of the progression from impaired glucose tolerance to type 2 diabetes

In a still further aspect, the present compounds are useful for the delaying or prevention of the progression from non-insulin requiring type 2 diabetes to insulin requiring type 2 diabetes

In another aspect, the present compounds reduce triglyceride levels and are accordingly useful for the treatment and/or prevention of ailments and disorders such as diabetes and/or obesity

In still another aspect, the present compounds are useful for the treatment and/or prophylaxis of insulin resistance, impaired glucose tolerance, dyslipidemia, disorders related to metabolic syndrome X such as hypertension, obesity, insulin resistance, hyperglycaemia, atherosclerosis, hyperlipidemia, coronary artery disease, myocardial ischemia and other cardiovascular disorders

The present compounds may also be administered in combination with one or more further pharmacologically active substances eg , selected from antiobesity agents, antidiabetics, antihypertensive agents, agents for the treatment and/or prevention of complications resulting from or associated with diabetes and agents for the treatment and/or prevention of complications and disorders resulting from or associated with obesity

Thus, in a further aspect of the invention the present compounds may be administered in combination with one or more antiobesity agents or appetite regulating agents

Such agents may be selected from the group consisting of CART (cocaine amphetamine regulated transcript) agonists, NPY (neuropeptide Y) antagonists, MC4 (melanocortin 4) agonists, orexin antagonists, TNF (tumor necrosis factor) agonists, CRF (corticotropin releasing factor) agonists, CRF BP (corticotropin releasing factor binding protein) antagonists, urocortin agonists, β3 agonists, MSH (melanocyte-stimulating hormone) agonists, MCH (melanocyte-concentrating hormone) antagonists, CCK (cholecystokinin) agonists, se-

rotonin re-uptake inhibitors, serotonin and noradrenaline re-uptake inhibitors, mixed s rotonin and noradrenergic compounds, 5HT (serotonin) agonists, bombesin agonists, galanin antagonists, growth hormone, growth hormone releasing compounds, TRH (thyreotropin releasing hormone) agonists, UCP 2 or 3 (uncoupling protein 2 or 3) modulators, leptin agonists, DA agonists (bromocriptin, doprexin), lipase/amylase inhibitors, RXR (retinoid X receptor) modulators or TR β agonists

In one embodiment of the invention the antiobesity agent is leptin

In another embodiment the antiobesity agent is dexamphetamine or amphetamine

In another embodiment the antiobesity agent is fenfluramine or dexfenfluramine

In still another embodiment the antiobesity agent is sibutramine

In a further embodiment the antiobesity agent is orlistat

In another embodiment the antiobesity agent is mazindol or phentermine

Suitable antidiabetics comprise insulin, GLP-1 (glucagon like peptide-1) derivatives such as those disclosed in WO 98/08871 to Novo Nordisk A/S, which is incorporated herein by reference as well as orally active hypoglycaemic agents

The orally active hypoglycaemic agents preferably comprise sulphonylureas, biguanides, meglitinides, glucosidase inhibitors, glucagon antagonists such as those disclosed in WO 99/01423 to Novo Nordisk A/S and Agouron Pharmaceuticals, Inc , GLP-1 agonists, potassium channel openers such as those disclosed in WO 97/26265 and WO 99/03861 to Novo Nordisk A/S which are incorporated herein by reference, DPP-IV (dipeptidyl peptidase-IV) inhibitors, inhibitors of hepatic enzymes involved in stimulation of gluconeogenesis and/or glycogenolysis, glucose uptake modulators, compounds modifying the lipid metabolism such as antihyperlipidemic agents and antilipidemic agents as HMG CoA inhibitors (statins), compounds lowering food intake, RXR agonists and agents acting on the ATP-dependent potassium channel of the β-cells

In one embodiment of the invention the present compounds are administered in combination with insulin

In a further embodiment the present compounds are administered in combination with a sulphonylurea eg tolbutamide, glibenclamide, glipizide or glicazide

In another embodiment the present compounds are administered in combination with a biguanide eg metformin

In yet another embodiment the present compounds are administered in combination with a meglitinide eg repaglinide or senaglinide

In a further embodiment the present compounds are administered in combination with an α-glucosidase inhibitor eg miglitol or acarbose

In another embodiment the present compounds are administered in combination with an agent acting on the ATP-dependent potassium channel of the β-cells eg tolbutamide, glibenclamide, glipizide, glicazide or repaglinide

Furthermore, the present compounds may be administered in combination with nateglinide

In still another embodiment the present compounds are administered in combination with an antihyperlipidemic agent or antilipidemic agent eg cholestyramine, colestipol, clofibrate, gemfibrozil, lovastatin, pravastatin, simvastatin, probucol or dextrothyroxine

In a further embodiment the present compounds are administered in combination with more than one of the above-mentioned compounds eg in combination with a sulphonylurea and metformin, a sulphonylurea and acarbose, repaglinide and metformin, insulin and a sulphonylurea, insulin and metformin, insulin, insulin and lovastatin, etc

Furthermore, the present compounds may be administered in combination with one or more antihypertensive agents Examples of antihypertensive agents are β-blockers such as alprenolol, atenolol, timolol, pindolol, propranolol and metoprolol, ACE (angiotensin converting enzyme) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, quinapril and ramipril, calcium channel blockers such as nifedipine, felodipine, nicardipine, isradipine, nimodipine, diltiazem and verapamil, and α-blockers such as doxazosin, urapidil, prazosin and terazosin Further reference can be made to Remington The Science and Practice of Pharmacy, 19th Edition, Gennaro, Ed , Mack Publishing Co , Easton, PA, 1995

It should be understood that any suitable combination of the compounds according to the invention with one or more of the above-mentioned compounds and optionally one or more further pharmacologically active substances are considered to be within the scope of the present invention

The present invention also relates to processes according to reaction schemes P_1 and P_2 for the preparation of the above said novel compounds, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts or pharmaceutically acceptable solvates

Pharmaceutical compositions

The compounds of the invention may be administered alone or in combination with pharma-ceutically acceptable carriers or excipients, in either single or multiple doses The pharmaceutical compositions according to the invention may be formulated with

pharmaceutically acceptable carriers or diluents as well as any other known adjuvants and excipients in accordance with conventional techniques such as those disclosed in Remington The Science and Practice of Pharmacy,19th Edition, Gennaro, Ed , Mack Publishing Co , Easton, PA, 1995 The compositions may appear in conventional forms, for example capsules, tablets, aerosols, solutions, suspensions or topical applications

The pharmaceutical compositions may be specifically formulated for administration by any suitable route such as the oral, rectal, nasal, pulmonary, topical (including buccal and sublingual), transdermal, intracisternal, intraperitoneal, vaginal and parenteral (including subcutaneous, intramuscular, intrathecal, intravenous and intradermal) route, the oral route being preferred It will be appreciated that the preferred route will depend on the general condition and age of the subject to be treated, the nature of the condition to be treated and the active ingredient chosen

Pharmaceutical compositions for oral administration include solid dosage forms such as capsules, tablets, dragees, pills, lozenges, powders and granules Where appropriate, they can be prepared with coatings such as enteric coatings or they can be formulated so as to provide controlled release of the active ingredient such as sustained or prolonged release according to methods well-known in the art

Liquid dosage forms for oral administration include solutions, emulsions, suspensions, syrups and elixirs

Pharmaceutical compositions for parenteral administration include sterile aqueous and non-aqueous injectable solutions, dispersions, suspensions or emulsions as well as sterile powders to be reconstituted in sterile injectable solutions or dispersions prior to use Depot injectable formulations are also contemplated as being within the scope of the present invention

Other suitable administration forms include suppositories, sprays, ointments, cremes, gels, inhalants, dermal patches, implants etc

The therapeutic dose of the compound will depend upon the frequency and mode of administration, the sex, age, weight and general condition of the subject treated, the nature and severity of the condition treated and any concomitant dis ases to be treated and other

factors evident to those skill d in the art The formulations may conveniently be presented in unit dosage form by methods known to those skilled in the art In one embodiment the composition in unit dosage form, comprises from about 0 05 to about 2000 mg, preferably from about 0 1 to about 500 mg of the compound of formula I pharmaceutically acceptable salt thereof

In a still further embodiment the pharmaceutical composition is for oral, nasal, transdermal, pulmonal, or parenteral administration

For parenteral routes, such as intravenous, intrathecal, intramuscular and similar administration, typically doses are in the order of about half the dose employed for oral administration

The compounds of this invention are generally utilized as the free substance or as a pharmaceutically acceptable salt thereof One example is an acid addition salt of a compound having the utility of a free base When a compound of the invention contains a free base such salts are prepared in a conventional manner by treating a solution or suspension of a free base of the compound with a chemical equivalent of a pharmaceutically acceptable acid, for example, inorganic and organic acids Representative examples are mentioned above Physiologically acceptable salts of a compound with a hydroxy group include the anion of said compound in combination with a suitable cation such as sodium or ammonium ion

For parenteral administration, solutions of the present compounds in sterile aqueous solution, aqueous propylene glycol or sesame or peanut oil may be employed Such aqueous solutions should be suitable buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose The aqueous solutions are particularly suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art

Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solution and various organic solvents Examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, peanut oil, olive oil, gelatine, lactose, terra alba, sucrose, cyclodextrin, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid or lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid st rs,

polyoxyethylene, hydroxymethylcellulose and polyvinylpyrrolidone Similarly, th carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavouring agents

The pharmaceutical compositions formed by combining the compounds of the invention and the pharmaceutically acceptable carriers are then readily administered in a variety of dosage forms suitable for the disclosed routes of administration The formulations may conveniently be presented in unit dosage form by methods known in the art of pharmacy

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules or tablets, each containing a predetermined amount of th active ingredient, and which may include a suitable excipient These formulations may be in th form of powder or granules, as a solution or suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion

If a solid carrier is used for oral administration, the preparation may be tabletted, placed in a hard gelatine capsule in powder or pellet form or it can be in the form of a troche or lozenge The amount of solid carrier will vary widely but will usually be from about 25 mg to about 1 g If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatine capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution

A typical tablet which may be prepared by conventional tabletting techniques may contain

Core	
Active compound (as free compound or salt thereof)	5 mg
Colloidal silicon dioxide (Aerosil)	1 5 mg
Cellulose, microcryst (Avicel)	70 mg
Modified cellulose gum (Ac-Di-Sol)	7 5 mg
Magnesium stearate	q s
Coating	
HPMC approx	9 mg
*Mywacett 9-40 T approx	0 9 mg

*Acylated monoglyceride used as plasticizer for film coating

The compounds of the invention may be administered to a patient which is a mammal, especially a human in need thereof Such mammals include also animals, both domestic animals, e g household pets, and non-domestic animals such as wildlife

In a further aspect of the invention the present compounds may be administered in combination with further pharmacologically active substances e g an antidiabetic or other pharmacologically active material, including other compounds for the treatment and/or prevention of insulin resistance and diseases, wherein insulin resistance is the pathophysiological mechanism

Furthermore, the compounds according to the invention may be administered in combination with antiobesity agents or appetite regulating agents

EXAMPLES

General procedure (A)

The arylboronic acid (1 mmol) and the diol (1 1 mmol) in toluene (10 mL) were stirred at room temperature for 2 h The organic phases was washed with water three tim s and subsequently evaporated and dried in vacuo

Gen ral procedure (B)

The arylboronic acid (1 mmol) and diethanolamine (1 1 mmol) in toluene (10 mL) were stirred at room temperature for 2 h The solution was evaporated to dryness and the resulting crystals were washed with heptane/iso-propanol (1 9) and dried in vacuo

Example 1 (General procedure (A))

2-(5-Chlorothiophen-2-yl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane

The title compound (50%, oil) was prepared from 5-chlorothiophen-2-boronic acid and pinacol

^{1}H NMR (300 MHz, $CDCl_3$) δ 1 32 (s, 12H), 6 96 (d, 1H), 7 40 (d, 1H)

Example 2 (General procedure (A))

2-(5-Chlorothiophen-2-yl)-5,5-dimethyl-[1,3,2]dioxaborinane

The title compound (54%, crystals) was prepared from 5-chlorothiophen-2-boronic acid and neopentylglycol

^{1}H NMR (300 MHz, $CDCl_3$) δ 1 04 (s, 6H), 3 74 (s, 4H), 6 95 (d, 1H), 7 32 (d, 1H)

Example 3 (General procedure (B))

2-(5-Chlorothiophen-2-yl)-[1,3,6,2]dioxazaborocane

The title compound (28%, crystals) was prepared from 5-chlorothiophen-2-boronic acid and diethanolamin

Mp 188-190 °C ^{1}H NMR (300 MHz, DMSO d_6) δ 2 82-2 92 (m, 2H), 3 01-3 15 (m, 2H), 3 71-3 88 (m, 4H), 6 81 (d, 1H), 6 93 (d, 1H), 7 09 (bs, 1H)

Example 4 (General procedure (B))

2-(3,5-Difluorophenyl)-[1,3,6,2]dioxazaborocane

The title compound (93%, crystals) was prepared from 3,5-difluorophenylboronic acid and diethanolamin

Mp 198-200 °C ^{1}H NMR (300 MHz, DMSO d_6) δ 2 76-2 84 (m, 2H), 3 18-3 30 (m, 2H), 3 92-4 10 (m, 4H), 6 64 (tt, 1H), 6 82 (bs, 1H), 7 05-7 12 (m, 1H)

Example 5 (General procedure (B))
2-(3-Bromophenyl)-[1,3,6,2]dioxazaborocane

The title compound (78%, crystals) was prepared from 3-bromophenylboronic acid and diethanolamin
Mp 208-212 °C ^{1}H NMR (300 MHz, $CDCl_3$) δ 2 76-2 86 (m, 2H), 3 18-3 31 (m, 2H), 3 94-4 10 (m, 4H), 4 68 (bs, 1H), 7 18(t, 1H), 7 38 (dt, 1H), 7 49 (m, 1H), 7 69 (bs, 1H)

Example 6 (General procedure (B))
2-(3-Chlorophenyl)-[1,3,6,2]dioxazaborocane

The title compound (79%, crystals) was prepared from 3-chlorophenylboronic acid and diethanolamin
Mp 235-238 °C ^{1}H NMR (300 MHz, $CDCl_3$) δ 2 68-2 77 (m, 2H), 3 12-3 27 (m, 2H), 3 86-4 02 (m, 4H), 4 98 (bs, 1H), 7 22(d, 2H), 7 42 (t, 1H), 7 52 (bs, 1H)

Example 7 (General procedure (B))
2-(3-Fluorophenyl)-[1,3,6,2]dioxazaborocane

The title compound (79%, crystals) was prepared from 3-fluorophenylboronic acid and diethanolamin
Mp 207-209 °C ^{1}H NMR (300 MHz, $CDCl_3$) δ 2 68-2 78 (m, 2H), 3 12-3 27 (m, 2H), 3 85-4 02 (m, 4H), 4 97 (bs, 1H), 6 89-6 98 (m, 1H), 7 21-7 31 (m, 3H)

Example 8 (General procedure (B))
2-(3-Trifluoromethylphenyl)-[1,3,6,2]dioxazaborocane

The title compound (79%, crystals) was prepared from 3-trifluoromethylphenylboronic acid and diethanolamin
Mp 188-192 °C ^{1}H NMR (300 MHz, $CDCl_3$) δ 2 77-2 88 (m, 2H), 3 20-3 33 (m, 2H), 3 95-4 11 (m, 4H), 4 68 (bs, 1H), 7 40(t, 2H), 7 52 (d, 1H), 7 77 (d, 1H), 7 84 (bs, 1H)

Example 9 (General procedur (B))
2-(3,4,5-Trifluorophenyl)-[1,3,6,2]dioxazaborocane

The title compound (70%, crystals) was prepared from 3,4,5-trifluorophenylboronic acid and diethanolamin
Mp 265-269 °C ^{1}H NMR (300 MHz, $CDCl_3$) δ 2 90-2 99 (m, 2H), 3 26-3 39 (m, 2H), 4 03-4 21 (m, 4H), 7 16(t, 2H)

Example 10 (General procedure (A))
2-(3-Chlorophenyl)-5,5-dimethyl-[1,3,2]dioxaborinane

The title compound (65%, crystals) was prepared from 3-chlorophenylboronic acid and neopentylglycol
Mp 80-83 °C ^{1}H NMR (300 MHz, $CDCl_3$) δ 1 03 (s, 6H), 3 78 (s, 4H), 7 27 (t, 1H), 7 39 (ddd, 1H), 7 66 (d, 1H), 7 77 (bs, 1H)

Example 11 (General procedure (A))
5,5-Dimethyl-2-(3-trifluoromethylphenyl)-[1,3,2]dioxaborinane

The title compound (58%, crystals) was prepared from 3-trifluoromethylphenylboronic acid and neopentylglycol
Mp 80-83 °C ^{1}H NMR (300 MHz, $CDCl_3$) δ 1 03 (s, 6H), 3 79 (s, 4H), 7 46 (t, 1H), 7 57 (d, 1H), 7 97 (d, 1H), 8 07 (bs, 1H)

Example 12 (General procedure (B))
2-(5-Chloro-2-methoxyphenyl)-[1,3,6,2]dioxazaborocane

The title compound (47%, crystals) was prepared from 5-chloro-2-methoxyphenylboronic acid and diethanolamin
Mp 183-188 °C ^{1}H NMR (300 MHz DMSO d_6) δ 2 73-2 85 (m, 2H), 3 12-3 27 (m, 2H), 3 59-3 70 (m, 2H), 3 68 (s, 3H), 3 76-3 85 (m, 2H), 6 79 (d, 2H), 7 14 (dd, 1H), 7 29 (d, 1H)

Example 13 (General procedure (B))
2-(3-Trifluoromethoxyphenyl)-[1,3,6,2]dioxazaborocane

The title compound (86%, crystals) was prepared from 3-trifluoromethoxyphenylboronic acid and diethanolamin

Mp 130-136 °C ^{1}H NMR (300 MHz DMSO d_6) δ 2 83-2 92 (m, 2H), 3 04-3 17 (m, 2H), 3 56-3 91 (m, 4H), 7 00 (bs, 1H), 7 11 (d, 1H), 7 28-7 36 (m, 2H), 7 43 (d, 1H)

Example 14 (General procedure (B))

2-(3,5-Dichlorophenyl)-[1,3,6,2]dioxazaborocane

The title compound (94%, crystals) was prepared from 3,5-dichlorophenylboronic acid and diethanolamin

Mp 238-242 °C ^{1}H NMR (300 MHz DMSO d_6) δ 2 85-2 92 (m, 2H), 3 06-3 18 (m, 2H), 3 76-3 90 (m, 4H), 7 07 (bs, 1H), 7 33 (s, 3H)

Example 15 (General procedure (B))

2-(3-Chloro-4-fluorophenyl)-[1,3,6,2]dioxazaborocane

The title compound (87%, oil) was prepared from 3-chloro-4-fluorophenylboronic acid and diethanolamin

^{1}H NMR (300 MHz DMSO d_6) δ 2 83-2 91 (m, 2H), 3 04-3 17 (m, 2H), 3 75-3 90 (m, 4H), 6 98 (bs, 1H), 7 20 (dd, 1H), 7 34-7 40 (m, 1H), 7 48 (dd, 1H)

Example 16 (General procedure (B))

2-(4-Methylthiophen-2-yl)-[1,3,6,2]dioxazaborocane

The title compound (88%, oil) was prepared from 4-methylthiophen-2-boronic acid and diethanolamin

^{1}H NMR (300 MHz DMSO d_6) δ 2 18 (s, 3H), 2 78-2 87 (m, 2H), 3 00-3 12 (m, 2H), 3 72-3 87 (m, 4H), 6 80 (s, 1H), 6 92 (s, 1H), 6 98 (bs, 1H)

Example 17 (General procedure (A))

2-(3-Bromophenyl)-5,5-dimethyl-[1,3,2]dioxaborinane

The title compound (86%, crystals) was prepared from 3-bromophenylboronic acid and neopentylglycol

^{1}H NMR (300 MHz, $CDCl_3$) δ 1 02 (s, 6H), 3 78 (s, 4H), 7 22 (t, 1H), 7 54 (dd, 1H), 7 70 (d, 1H), 7 93 (bs, 1H)

Example 18 (General procedure (A))

2-(5-Chloro-2-methoxyphenyl)-5,5-dimethyl-[1,3,2]dioxaborinane

The title compound (86%, oil) was prepared from 5-chloro-2-methoxyphenylboronic acid and neopentylglycol

^{1}H NMR (300 MHz, $CDCl_3$) δ 1 04 (s, 6H), 3 79 (s, 4H), 3 81 (s, 3H), 6 79 (d, 1H), 7 30 (dd, 1H), 7 60 (d, 1H)

Example 19 (General procedure (A))

5,5-Dimethyl-2-(3,4,5-trifluorophenyl)-[1,3,2]dioxaborinane

The title compound (34%,yellow oil) was prepared from 3,4,5-trifluorophenylboronic acid and neopentylglycol

^{1}H NMR (300 MHz, $CDCl_3$) δ 1 01 (s, 6H), 3 77 (s, 4H), 7 38 (t, 3H)

^{1}H NMR (300 MHz DMSO d_6) δ 2 78-2 87 (m, 2H), 3 00-3 12 (m, 2H), 3 72-3 87 (m, 4H), 6 80 (s, 1H), 6 92 (s, 1H), 6 98 (bs, 1H)

Example 20 (General procedure (A))

5,5-Dimethyl-2-(3-trifluoromethoxyphenyl)-[1,3,2]dioxaborinane

The title compound (64%, oil) was prepared from 3-trifluoromethoxyphenylboronic acid and neopentylglycol

^{1}H NMR (300 MHz, $CDCl_3$) δ 1 03 (s, 6H), 3 78 (s, 4H), 7 26 (bd, 1H), 7 38 (t, 1H), 7 62 (bs, 1H), 7 71 (d, 1H)

Example 21 (General procedure (A))

2-(3,5-Dichlorophenyl)-5,5-dimethyl-[1,3,2]dioxaborinane

The title compound (80%, crystals) was prepared from 3,5-dichlorophenylboronic acid and neopentylglycol

^{1}H NMR (300 MHz, $CDCl_3$) δ 1 03 (s, 6H), 3 77 (s, 4H), 7 40 (t, 1H), 7 63 (d, 2H)

Exampl 22 (General procedure (A))
2-(3-Chloro-4-fluorophenyl)-5,5-dimethyl-[1,3,2]dioxaborinane

The title compound (80%, crystalsl) was prepared from 3-chloro-4-fluorophenylboronic acid and neopentylglycol
^{1}H NMR (300 MHz, $CDCl_3$) δ 1 03 (s, 6H), 3 77 (s, 4H), 7 10 (dd, 1H), 7 65 (dd, 1H), 7 82 (dd, 1H)

Example 23 (General procedure (A))
2-(3-Fluorophenyl)-5,5-dimethyl-[1,3,2]dioxaborinane

The title compound (55%, oil) was prepared from 3-trifluorophenylboronic acid and neopentylglycol
^{1}H NMR (300 MHz, $CDCl_3$) δ 1 02 (s, 6H), 3 78 (s, 4H), 7 09 (dt, 1H), 7 28-7 36 (m, 1H), 7 46 (dd, 1H), 7 56 (d, 1H)

Example 24 (General procedure (A))
5,5-Dimethyl-2-(4-methylthiophen-2-yl)-[1,3,2]dioxaborinane

The title compound (60%, yellow crystals) was prepared from 4-methylthiophen-2-boronic acid and neopentylglycol
^{1}H NMR (300 MHz, $CDCl_3$) δ 1 03 (s, 6H), 2 28 (s, 3H), 3 77 (s, 4H), 7 13 (d, 1H), 7 37 (d, 1H)

Example 25 (General procedure (A))
2-(3-Bromophenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane

The title compound (77%, oil) was prepared from 3-bromophenylboronic acid and pinacol
^{1}H NMR (300 MHz, $CDCl_3$) δ 1 35 (s, 12H), 7 23 (t, 1H), 7 58 (dd, 1H), 7 70 (d, 1H), 7 93 (bs, 1H)

Example 26 (General procedure (A))
2-(5-Chloro-2-methoxyphenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane

The title compound (57%, oil) was prepared from 5-chloro-2-m thoxyphenylboronic acid and pinacol

^{1}H NMR (300 MHz, $CDCl_3$) δ 1 35 (s, 12H), 3 81 (s, 3H), 6 86 (d, 1H), 7 38 (dd, 1H), 7 80 (d, 1H)

Example 27 (General procedure (A))

4,4,5,5-Tetramethyl-2-(3-trifluoromethoxyphenyl)-[1,3,2]dioxaborolane

The title compound (25%, oil) was prepared from 3-trifluoromethoxyphenylboronic acid and pinacol

^{1}H NMR (300 MHz, $CDCl_3$) δ 1 35 (s, 12H), 7 30 (d, 1H), 7 40 (t, 1H), 7 64 (bs, 1H), 7 72 (d, 1H)

Example 28 (General procedure (A))

2-(3,5-Dichlorophenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane

The title compound (73%, oil) was prepared from 3,5-dichlorophenylboronic acid and pinacol

^{1}H NMR (300 MHz, $CDCl_3$) δ 1 35 (s, 12H), 7 43 (t, 1H), 7 67 (d, 2H)

Example 29 (General procedure (A))

2-(3-Chloro-4-fluorophenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane

The title compound (77%, oil) was prepared from 3-chloro-4-fluorophenylboronic acid and pinacol

^{1}H NMR (300 MHz, $CDCl_3$) δ 1 34 (s, 12H), 7 12 (dd, 1H), 7 67 (ddd, 1H), 7 86 (dd, 1H)

Example 30 (General procedure (A))

2-(3-Chlorophenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane

The title compound (75%, oil) was prepared from 3-chlorophenylboronic acid and pinacol

^{1}H NMR (300 MHz, $CDCl_3$) δ 1 36 (s, 12H), 7 30 (t, 1H), 7 42 (dt, 1H), 7 68 (d, 1H), 7 78 (bd, 1H)

Exampl 31 (General procedure (A))

4,4,5,5-Tetramethyl-2-(3-trifluoromethylphenyl)-[1,3,2]dioxaborolane

The title compound (47%, oil) was prepared from 3-trifluoromethylphenylboronic acid and pinacol

^{1}H NMR (300 MHz, $CDCl_3$) δ 1 35 (s, 12H), 7 48 (t, 1H), 7 70 (d, 1H), 7 97 (d, 1H), 8 06 (bs, 1H)

Example 32 (General procedure (A))

4,4,5,5-Tetramethyl-2-(4-methylthiophen-2-yl)-[1,3,2]dioxaborolane

The title compound (54%, oil) was prepared from 4-methylthiophen-2-yl-boronic acid and pinacol

^{1}H NMR (300 MHz, $CDCl_3$) δ 1 34 (s, 12H), 2 29 (s, 3H), 7 20 (s, 1H), 7 44 (s, 1H)

Example 33 (commercially available compound)

4-Benzyloxyphenylboronic acid

Example 34 (commercially available compound)

4-BROMOBENZENEBORONIC ACID N-METHYLDIETHANOLAMINE CYCLIC ESTER

Example 35 (commercially available compound)

2-(3,5-DIFLUOROPHENYL)-5,5-DIMETHYL-1,3,2-DIOXABORINANE

Example 36 (commercially available compound)

3-BROMOBENZENEBORONIC ACID N-METHYLDIETHANOLAMINE CYCLIC ESTER

Example 37 (commercially available compound)

2-(4-BROMOPHENYL)-5,5-DIMETHYL-1,3,2-DIOXABORINANE

Example 38 (commercially available compound)

2-(2-chloroPHENYL)-5,5-DIMETHYL-1,3,2-DIOXABORINANE

Example 39 (commercially available compound)

2-(5,5-Dimethyl-[1,3,2]dioxaborinan-2-yl)-benzonitrile

Example 40 (commercially available compound)
2-(2-Fluoro-phenyl)-5,5-dimethyl-[1,3,2]dioxaborinane

Example 42 (commercially available compound)
2-(5,5-Dimethyl-[1,3,2]dioxaborinan-2-yl)-benzoic acid ethyl ester

Example 43 (commercially available compound)
5-CHLORO-2-METHOXYPHENYLBORONIC ACID

Example 44 (commercially available compound)
3,5-Dibromophenylboronic acid

Example 45 (commercially available compound)
3-Ethoxyphenylboronic acid

Example 46 (commercially available compound)
3-phenylphenylboronic acid

Example 47 (commercially available compound)
4-fluorophenylboronic acid

Example 48 (commercially available compound)
2-Bromophenylboronic acid

Example 49 (commercially available compound)
3-Bromophenylboronic acid

Example 50 (commercially available compound)
2,6-Dichlorophenylboronic acid

Example 51 (commercially available compound)
3-Methylphenylboronic acid

Example 52 (commercially available compound)
2-Chlorophenylboronic acid

Example 53 (commercially available compound)
3-Chlorophenylboronic acid

3-(TRIFLUOROMETHOXY)BENZENEBORONIC ACID

Example 55 (commercially available compound)
3-Trifluoromethylphenylboronic acid

Example 56 (commercially available compound)
3,5-Bis(Trifluoromethyl)phenylboronic acid

Example 57 (commercially available compound)
3,5-Dichlorophenylboronic acid

Example 58 (commercially available compound)
3-Chloro-4-fluorophenylboronic acid

Example 59 (commercially available compound)
3,5-Difluorophenylboronic acid

Example 60 (commercially available compound)
3-Fluorophenylboronic acid

Example 61 (commercially available compound)
2,3-DIFLUORO-4-PENTYLPHENYLBORONIC ACID

Example 62 (commercially available compound)

(3-FLUORO-4-BENZYLOXYPHENYL)BORONIC ACID

Example 63 (commercially available compound)
3,4,5-Trifluorophenylboronic acid

Example 64 (commercially available compound)
2,3,5-Trichlorophenylboronic acid

Example 65 (commercially available compound)
2,5-Dichlorophenylboronic acid

Example 66 (commercially available compound)
2,3-Difluorophenylboronic acid

Example 67 (commercially available compound)

2,5-Difluorophenylboronic acid

Example 68 (commercially available compound)
4'-(4,4,5,5-TETRAMETHYL-1,3,2-DIOXABOROLAN-2-YL)ACETANILIDE

Example 69 (commercially available compound)

3,4-Difluorophenylboronic acid

Example 70 (commercially available compound)
2,3-Dichlorophenylboronic acid

Example 71 (commercially available compound)
2,3-Difluoro-4-bromophenylboronic acid

Example 72 (commercially available compound)
3-Fluoro-4-phenylboronic acid

Example 73 (commercially available compound)
2-Methoxy5-fluorophenylboronic acid

Example 74 (commercially available compound)
3,4-Dichlorophenylboronic acid

Example 75 (commercially available compound)
5-INDOLYL BORONIC ACID

Example 76 (commercially available compound)
3-Formylphenylboronic acid

Example 77 (commercially available compound)
4-(N,N-DIMETHYLCARBAMOYL)PHENYLBORONIC ACID

Exampl 78 (commercially available compound)
6-Methoxy-2-phenyl-hexahydro-pyrano[3,2-a][1,3,2]dioxaborinine-7,8-diol

Example 79 (commercially available compound)
2-Fluoro-4-(5-pentyl-[1,3,2]dioxaborinan-2-yl)-benzoic acid

Example 80 (commercially available compound)
4-(3-Iodo-phenoxymethyl)-2-phenyl-[1,3,2]dioxaborolane

Example 81 (commercially available compound)
3'-(4,4,5,5-TETRAMETHYL-1,3,2-DIOXABOROLAN-2-YL)-2-trimethylsilylthiophen

Example 82 (commercially available compound)
4'-(4,4,5,5-TETRAMETHYL-1,3,2-DIOXABOROLAN-2-YL)2-nitrothiophene

Example 83 (commercially available compound)
1-BENZOTHIOPHEN-3-YLBORONIC ACID

Example 84 (commercially available compound)
2-FORMYL-3-THIOPHENEBORONIC ACID

Example 85 (commercially available compound)
2-THIEN-3-YL-1,3,2-BENZODIOXABOROLE

Example 86 (commercially available compound)
3-Thiophenboronic acid

Exampl 87 (commercially available compound)
2-(2-FORMYL-3-METHYLTHIEN-5-YL)-1,3,2-DIOXABORINANE

Example 88 (commercially available compound)
4-METHYLTHIOPHENE-2-BORONIC ACID

Example 89 (commercially available compound)
5-METHYLFURAN-2-BORONIC ACID

Example 90 (commercially available compound)
5-Methylthiophene-2-boronic acid

Example 91 (commercially available compound)
BENZO[B]FURAN-2-BORONIC ACID

Example 92 (commercially available compound)
Benzo[B]thiophene-2-boronic acid

Example 93 (commercially available compound)
Furan-2-boronic acid

Example 94 (commercially available compound)
5-Chlorothiophene-2-boronic acid

Example 95 (commercially available compound)
5-Cyanothiophene-2-boronic acid

Example 96 (commercially available compound)
5-Acetylthiophene-2-boronic acid

Example 97 (commercially available compound)
Thiophene-2-boronic acid

Example 98 (commercially available compound)
3-Bromothiophene-2-boronic acid

Example 99 (commercially available compound)
5,5-Dimethyl-2-(3-iodothiophen-2-yl)-[1,3,2]dioxaborinane

PHARMACOLOGICAL METHODS

3180 2 Assay for determination of percent inhibition by compound at 10 μM concentration

A lipid emulsion with ^{3}H-Triolein and phospholipid is used as substrate with a standard cencentration of highly purified HSL BSA is added as product receptor The substrate is prepared as follows
30 µl PC PI (20 mg/ml solution of PC PI 3 1 prepared in chloroform) + 128 µl cold TO + 15 µl ^{3}H-TO are mixed and then evaporated under a gentle stream of N_2 followed by 20-30 minutes in a Speedvac to ensure the absence of residual solvent
Compound and HSL are incubated for 30 min at 25 °C before addition of substrate Reaction is stopped after 30 min at 25 °C by adding a mixture of methanol, chloroform and heptane at high pH Formed product is separated from substrate by phase separation
Results are given as percent activity relative to an un-inhibited sample (no compound)

3190 1 Assay for determination of percent inhibition of hormone sensitive lipase by compound at 10µM sample concentration

A lipid emulsion with fluorochrome-labeled triacylglyceride and phospholipid is used as substrate with a standard concentration of highly purified HSL (12µg/mL initial concentration corresponding to 600ng/mL final concentration) BSA is added as product receptor The transfer of the fluorochrome from the lipid phase to the water (BSA) phase changes the fluorescent properties of the fluorochrome The changes can be monitored on a fluorimeter with an excitation wavelength of 450nm and an emission wavelength of 545nm

Compound and HSL (20µL compound, 10µL enzyme and 70µL PED-BSA buffer) is pr - incubated for 30min at 25°C before addition of substrate (100µL) Amount of formed product is measured after 120min incubation at 37°C

Results are given as percent activity relative to a non-inhibited sample (no compound)

3180 1 Assay for determination of inhibitor IC_{50} values

A lipid emulsion with ^{3}H-Triolein and phospholipid is used as substrate with a standard cencentration of highly purified HSL BSA is added as product receptor The substrate is prepared as follows

30 µl PC PI (20 mg/ml solution of PC PI 3 1 prepared in chloroform) + 128 µl cold TO + 15 µl ^{3}H-TO are mixed and then evaporated under a gentle stream of N_2 followed by 20-30 minutes in a Speedvac to ensure the absence of residual solvent

Compound and HSL are incubated for 30 min at 25 °C before addition of substrate Reaction is stopped after 30 min at 25 °C by adding a mixture of methanol, chloroform and heptane at high pH Formed product is separated from substrate by phase separation

Standard concentrations of compound are 100μM, 20μM, 4μM, 0 8μM, 0 16μM and 0 032μM (sample concentrations)

Results are given as IC_{50} values after 4PL fit of obtained activity data

3190 2 Assay for determination of IC_{50} value for the inhibition of hormone sensitive lipase by compound Standard concentrations of compound are 100μM and 5-fold dilutions (initial concentration corresponding to 10μM final concentration and 5-fold)

A lipid emulsion with fluorochrome-labeled triacylglyceride and phospholipid is used as substrate with a standard concentration of highly purified HSL (12µg/mL initial concentration corresponding to 600ng/mL final concentration) BSA is added as product receptor The transfer of the fluorochrome from the lipid phase to the water (BSA) phase changes the fluorescent properties of the fluorochrome The changes can be monitored on a fluorimeter with an excitation wavelength of 450nm and an emission wavelength of 545nm

Compound and HSL (20µL compound, 10µL enzyme and 70µL PED-BSA buffer) is pre-incubated for 30min at 25°C before addition of substrate (100µL) Amount of formed product is measured after 120min incubation at 37°C

Results are given as IC_{50} values after 4PL fit of obtained activity data

COMPOUND ACCORDING TO EXAMPLE #	TEST 3190 1 HSL-FL Activity (%)	TEST 3180 2 HSL Activity (%)
1	17	
2	17	
3	19	
4	32	
5	34	
6	36	
7	80	
8	29	
9	32	
10	39	
11	31	
12	39	
13	26	
14	40	
15	39	
16	61	
17	11	
18	43	
19	49	
20	27	
21	42	
22	31	
23	46	
24	58	
25	28	
27	29	
28	43	
29	36	
30	40	
31	27	
32	52	

33		85
34		81
35		38
36		43
37		83
38		89
39		97
40		68
42		93
43		36
44		71
45		90
46		96
47		65
48		81
49		33
50		88
51		64
52		86
53		34
54		27
55		21
56		89
57		46
58		35
59		25
60		47
61		85
62		93
63		26
64		76
65		55
66		55
67		34

68		86
69		45
70		66
71		61
72		97
73		62
74	53	
75	100	
76	80	
77	98	
78		82
79		100
80		80
81		85
82		96
83		76
84		92
85		89
87		75
88		49
89		87
90		48
91		57
92		53
93		89
94		17
95		49
96		68
97		66
98		84

CLAIMS

1 Use of a boronic acid, an ester thereof, a prodrug thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof for
a) inhibition of the lipolytic activity of hormone-sensitive lipase against triacylglycerols, diacylglycerols, cholesterol acyl esters or steroid acyl esters, and/or
b) modulating the plasma level of free fatty acids, glycerol, LDL-cholesterol, HDL-cholesterol, insulin and/or glucose, and/or
c) modulating intracellular triacylglycerol and cholesterol ester stores, intracellular level of fatty acids, fatty acid esters such as diacylglycerols, phosphatidic acids, long chain acyl-CoA´s as well as citrate or malonyl-CoA, and/or
d) increasing insulin sensitivity in adipose tissue, skeletal muscle, liver or pancreatic β cells, and/or
e) modulating insulin secretion from pancreatic β cells, and/or
f) inhibition of male fertility
in a patient

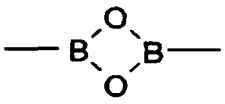
2 Use of a boronic acid, an ester thereof, a prodrug thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof for the preparation of a medicament for the treatment of any disorder where it is desirable to
a) inhibit the lipolytic activity of hormone-sensitive lipase against triacylglycerols, diacylglycerols, cholesterol acyl esters or steroid acyl esters, and/or
b) modulate the plasma level of free fatty acids, glycerol, LDL-cholesterol, HDL-cholesterol, insulin and/or glucose, and/or
c) modulate intracellular triacylglycerol and cholesterol ester stores, intracellular level of fatty acids, fatty acid esters such as diacylglycerols, phosphatidic acids, long chain acyl-CoA´s as well as citrate or malonyl-CoA, and/or
d) increase insulin sensitivity in adipose tissue, skeletal muscle, liver or pancreatic β cells, and/or
) modulate insulin secretion from pancreatic β cells, and/or
f) inhibit male fertility
in a patient

3 The use according to any one of claims 1-2, wherein pK_a of said boronic acid, an ester thereof, a prodrug thereof or a pharmaceutically acceptable salt thereof is betwe n 2 0 and

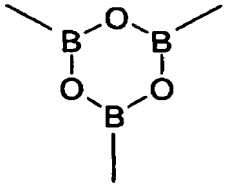
11 5, between 3 0 and 10 5, between 4 0 and 9 5, between 5 0 and 8 5, preferably between 5 5 to 8 0, and most preferable between 6 0 to 7 5

4 The use according to any one of claims 1-3, wherein the boronic acid, an ester thereof or a prodrug thereof is a dimer or trimer of a boronic acid

5 The use according to claim 4, wherein said dimer or trimer of a boronic acid comprises a structure selected from

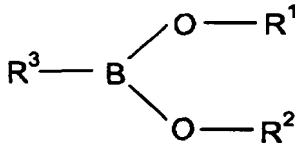


and



6 The use according to any one of claims 1-5, wherein said boronic acid, an ester thereof or a prodrug thereof comprises an atom selected from the group consisting of S, P, I, Br, Si, Se and Ge

7 The use according to any one of claims 1-5, wherein said boronic acid, an ester thereof or a prodrug thereof is of the general formula I



(I)

wherein R^1 and R^2 are independently selected from hydrogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfonyl, sulfinyl, amino, imino, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-

alkynyl, aryl, heteroaryl, C_{3-8}-het rocyclyl and C_{3-10}-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfonyl, sulfinyl, amino, imino, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfonyl, sulfinyl, amino, imino, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-h terocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfonyl, sulfinyl, amino, imino, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl,

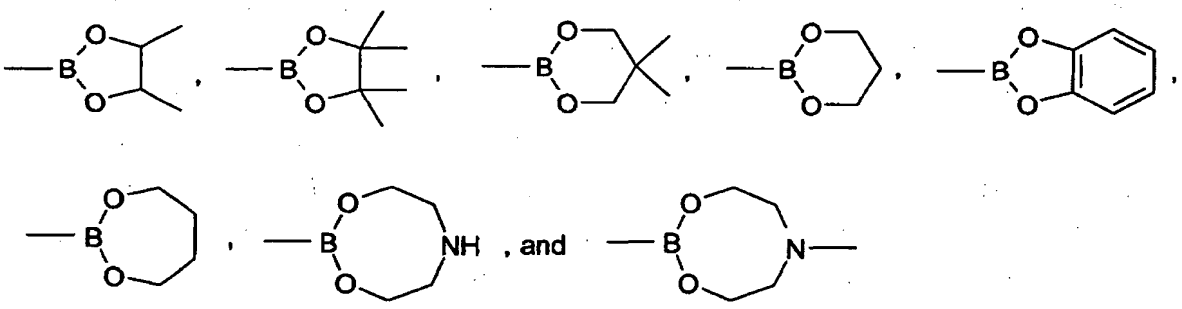
wherein R^2 is optionally covalently bound to R^1 by one or two ether, thioether, O-B, C-C, C=C or C-N bonds, to form a ring system with the O-atoms to which R^1 and R^2 are bound, and

R^3 is selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfonyl, sulfinyl, amino, imino, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfonyl, sulfinyl, amino, imino, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-

cycloalkyl, wherein each of hydroxy, sulfanyl, sulfonyl, sulfinyl, amino, imino, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfonyl, sulfinyl, amino, imino, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfonyl, sulfinyl, amino, imino, silyl, boranyl, C_{1-6}-alkyl, $C_{2\,6}$-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl,

or any tautomeric forms, stereoisomers, mixture of stereoisomers including a racemic mixture, oligomers or polymorphs

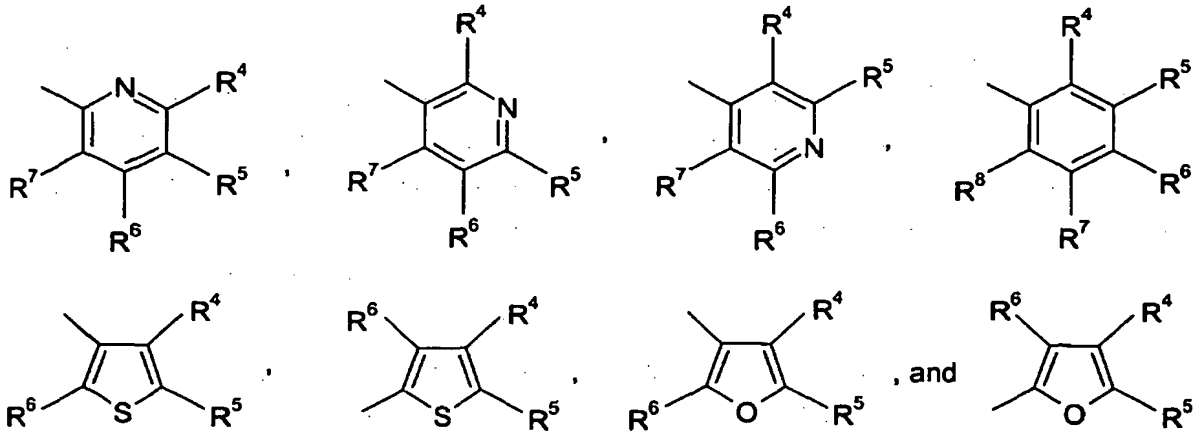
8 The use according to any one of claims 1-7, wherein said boronic acid, an ester thereof, or a prodrug thereof, comprises a structure selected from the group consisting of



9 The use according to any one of claims 7-8, wherein the group R^3 in the general formula (I) comprises an optionally substituted moiety selected from the group consisting of pyrrolidine-2-yl, pyrrolidine-3-yl, pyrrole-2-yl, pyrrole-3-yl, 3H-pyrrole-2-yl, 3H-pyrrole-3-yl, 3H-pyrrole-4-yl, 3H-pyrrole-5-yl, oxolane-2-yl, oxolane-3-yl, furane-2-yl, furane-3-yl, thiolane-2-yl, thiolane-3-yl, thiophene-2-yl, thiophene-3-yl, pyrazole-3-yl, pyrazole-4-yl, pyrazol -5-yl, pyra-

zolidine-3-yl, pyrazolidine-4-yl, imidazole-2-yl, imidazole-4-yl, imidazole-5-yl, imidazolidine-2-yl, imidazolidine-4-yl, 3H-pyrazole-3-yl, 3H-pyrazole-4-yl, 3H-pyrazole-5-yl, isoxazole-3-yl, isoxazole-4-yl, isoxazole-5-yl, oxazole-2-yl, oxazole-4-yl, oxazole-5-yl, isothiazole-3-yl, isothiazole-4-yl, isothiazole-5-yl, thiazole-2-yl, thiazole-4-yl, thiazole-5-yl, 1,2,5-oxadiazole-3-yl, 1,3,5-oxadiazole-2-yl, 1,3,5-oxadiazole-4-yl, 1,3,4-oxadiazole-2-yl, 1,2,3,5-oxatriazole-4-yl, 1,2,5-thiadiazole-3-yl, 1,3,5-thiadiazole-2-yl, 1,3,5-thiadiazole-4-yl, 1,3,4-thiadiazole-2-yl, 1,2,3,5-thiatriazole-4-yl, 1,2,3-triazole-4-yl, 1,2,3-triazole-5-yl, 1,2,4-triazole-3-yl, 1,2,4-triazole-5-yl, 1,2,5-triazole-3-yl, tetrazole-5-yl, 1,3-oxathiole-2-yl, 1,3-oxathiole-4-yl, 1,3-oxathiole-5-yl, benzofurane-2-yl, benzofurane-3-yl, isobenzofurane-1-yl, benzothiophene-2-yl, benzothiophene-3-yl, isobenzothiophene-1-yl, 1H-indole-2-yl, 1H-indole-3-yl, 2H-isoindole-1-yl, indolizine-1-yl, indolizine-2-yl, indolizine-3-yl, 1H-benzimidazole-2-yl, 1H-benzothiazole-2-yl, 1H-benzoxazole-2-yl, 1H-benzisooxazole-3-yl, 3H-indazole-3-yl, piperedine-1-yl, piperedine-2-yl, piperedine-3-yl, piperedine-4-yl, piperazine-1-yl, piperazine-2-yl, 2,5-dione-piparazine-1-yl, 2,5-dione-piparazine-3-yl and phenyl

10 The use according to any one of claims 7-9, wherein the group R^3 is selected from the group consisting of



, and

wherein R^4, R^5, R^6, R^7 and R^8 are independently selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfonyl, sulfinyl, amino, imino, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-

alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents indep ndently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfonyl, sulfinyl, amino, imino, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfonyl, sulfinyl, amino, imino, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl

11 The use according to claim 10, wherein the molar weight of each of R^4, R^5, R^6, R^7 and R^8 are below about 100 Dalton, preferably below about 80 Dalton, more preferable below 50 Dalton and even more preferable below about 20 Dalton

12 The use according to claim 10, wherein R^4, R^5, R^6, R^7 and R^8 are independently selected from hydrogen, halogen, hydroxyl, perhalomethyl, perhalomethoxy, C_{1-6}-alkyl, C_{1-6}-alkoxy and C_{1-6}-alkylthio

13 The use according to claim 10, wherein R^4, R^5, R^6, R^7 and R^8 are independently selected from hydrogen, halogen, methyl, methoxy, thiomethoxy, perhalomethyl, perhalomethoxy

14 The use according to claim 10, wherein R^4, R^5, R^6, R^7 and R^8 are independently selected from hydrogen, halogen, trifluoromethyl and trifluoromethoxy

15 The use according to any one of claims 7-14, wherein the group R^1 is H

16 The use according to any one of claims 7-15, wherein the group R^1 is H and the group R^2 is H

17 The use according to any one of claims 1-16, wherein said boronic acid, an ester thereof or a prodrug thereof is selected from the group consisting of
2-(5-Chlorothiophen-2-yl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane,
2-(5-Chlorothiophen-2-yl)-5,5-dimethyl-[1,3,2]dioxaborinane,
2-(5-Chlorothiophen-2-yl)-[1,3,6,2]dioxazaborocane,
2-(3,5-Difluorophenyl)-[1,3,6,2]dioxazaborocane,
2-(3-Bromophenyl)-[1,3,6,2]dioxazaborocane,
2-(3-Chlorophenyl)-[1,3,6,2]dioxazaborocane,
2-(3-Fluorophenyl)-[1,3,6,2]dioxazaborocane,
2-(3-Trifluoromethylphenyl)-[1,3,6,2]dioxazaborocane,
2-(3,4,5-Trifluorophenyl)-[1,3,6,2]dioxazaborocane,
2-(3-Chlorophenyl)-5,5-dimethyl-[1,3,2]dioxaborinane,
5,5-Dimethyl-2-(3-trifluoromethylphenyl)-[1,3,2]dioxaborinane,
2-(5-Chloro-2-methoxyphenyl)-[1,3,6,2]dioxazaborocane,
2-(3-Trifluoromethoxyphenyl)-[1,3,6,2]dioxazaborocane,
2-(3,5-Dichlorophenyl)-[1,3,6,2]dioxazaborocane,
2-(3-Chloro-4-fluorophenyl)-[1,3,6,2]dioxazaborocane,
2-(4-Methylthiophen-2-yl)-[1,3,6,2]dioxazaborocane,
2-(3-Bromophenyl)-5,5-dimethyl-[1,3,2]dioxaborinane,
2-(5-Chloro-2-methoxyphenyl)-5,5-dimethyl-[1,3,2]dioxaborinane,
5,5-Dimethyl-2-(3,4,5-trifluorophenyl)-[1,3,2]dioxaborinane,
5,5-Dimethyl-2-(3-trifluoromethoxyphenyl)-[1,3,2]dioxaborinane,
2-(3,5-Dichlorophenyl)-5,5-dimethyl-[1,3,2]dioxaborinane,
2-(3-Chloro-4-fluorophenyl)-5,5-dimethyl-[1,3,2]dioxaborinane,
2-(3-Fluorophenyl)-5,5-dimethyl-[1,3,2]dioxaborinane,
5,5-Dimethyl-2-(4-methylthiophen-2-yl)-[1,3,2]dioxaborinane,
2-(3-Bromophenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane,
2-(5-Chloro-2-methoxyphenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane,
4,4,5,5-Tetramethyl-2-(3-trifluoromethoxyphenyl)-[1,3,2]dioxaborolane,
2-(3,5-Dichloroph nyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane,
2-(3-Chloro-4-fluorophenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane,

2-(3-Chlorophenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane,
4,4,5,5-Tetramethyl-2-(3-trifluoromethylphenyl)-[1,3,2]dioxaborolane,
4,4,5,5-Tetramethyl-2-(4-methylthiophen-2-yl)-[1,3,2]dioxaborolane,
4-Benzyloxyphenylboronic acid,
4-BROMOBENZENEBORONIC ACID N-METHYLDIETHANOLAMINE CYCLIC ESTER,
2-(3,5-DIFLUOROPHENYL)-5,5-DIMETHYL-1,3,2-DIOXABORINANE,3-BROMOBENZENEBORONIC ACID N-METHYLDIETHANOLAMINE CYCLIC ESTER,
2-(4-BROMOPHENYL)-5,5-DIMETHYL-1,3,2-DIOXABORINANE,
2-(2-chloroPHENYL)-5,5-DIMETHYL-1,3,2-DIOXABORINANE,
2-(5,5-Dimethyl-[1,3,2]dioxaborinan-2-yl)-benzonitrile,
2-(2-Fluoro-phenyl)-5,5-dimethyl-[1,3,2]dioxaborinane,
2-(5,5-Dimethyl-[1,3,2]dioxaborinan-2-yl)-benzoic acid ethyl ester,
5-CHLORO-2-METHOXYPHENYLBORONIC ACID,
3,5-Dibromophenylboronic acid,
3-Ethoxyphenylboronic acid,
3-phenylphenylboronic acid,
4-fluorophenylboronic acid,
2-Bromophenylboronic acid,
3-Bromophenylboronic acid,
2,6-Dichlorophenylboronic acid,
3-Methylphenylboronic acid,
2-Chlorophenylboronic acid,
3-Chlorophenylboronic acid,
3-(TRIFLUOROMETHOXY)BENZENEBORONIC ACID,
3-Trifluoromethylphenylboronic acid,
3,5-Bis(Trifluoromethyl)phenylboronic acid,
3,5-Dichlorophenylboronic acid,
3-Chloro-4-fluorophenylboronic acid,
3,5-Difluorophenylboronic acid,
3-Fluorophenylboronic acid,
2,3-DIFLUORO-4-PENTYLPHENYLBORONIC ACID,
(3-FLUORO-4-BENZYLOXYPHENYL)BORONIC ACID,
3,4,5-Trifluorophenylboronic acid,
2,3,5-Trichlorophenylboronic acid,
2,5-Dichlorophenylboronic acid,

2,3-Difluorophenylboronic acid,
2,5-Difluorophenylboronic acid,
4'-(4,4,5,5-TETRAMETHYL-1,3,2-DIOXABOROLAN-2-YL)ACETANILIDE,
3,4-Difluorophenylboronic acid,
2,3-Dichlorophenylboronic acid,
2,3-Difluoro-4-bromophenylboronic acid,
3-Fluoro-4-phenylboronic acid,
2-Methoxy5-fluorophenylboronic acid,
3,4-Dichlorophenylboronic acid,
5-INDOLYL BORONIC ACID,
3-Formylphenylboronic acid,
4-(N,N-DIMETHYLCARBAMOYL)PHENYLBORONIC ACID,
6-Methoxy-2-phenyl-hexahydro-pyrano[3,2-a][1,3,2]dioxaborinine-7,8-diol,
2-Fluoro-4-(5-pentyl-[1,3,2]dioxaborinan-2-yl)-benzoic acid,
4-(3-Iodo-phenoxymethyl)-2-phenyl-[1,3,2]dioxaborolane,
3'-(4,4,5,5-TETRAMETHYL-1,3,2-DIOXABOROLAN-2-YL)-2-trimethylsilylthiophen,
4'-(4,4,5,5-TETRAMETHYL-1,3,2-DIOXABOROLAN-2-YL)2-nitrothiophene,
1-BENZOTHIOPHEN-3-YLBORONIC ACID,
2-FORMYL-3-THIOPHENEBORONIC ACID,
2-THIEN-3-YL-1,3,2-BENZODIOXABOROLE,
3-Thiophenboronic acid,
2-(2-FORMYL-3-METHYLTHIEN-5-YL)-1,3,2-DIOXABORINANE,
4-METHYLTHIOPHENE-2-BORONIC ACID,
5-METHYLFURAN-2-BORONIC ACID,
5-Methylthiophene-2-boronic acid,
BENZO[B]FURAN-2-BORONIC ACID,Benzo[B]thiophene-2-boronic acid,Furan-2-boronic acid,5-Chlorothiophene-2-boronic acid,5-Cyanothiophene-2-boronic acid,5-Acetylthiophene-2-boronic acid,Thiophene-2-boronic acid,3-Bromothiophene-2-boronic acid and5,5-Dimethyl-2-(3-iodothiophen-2-yl)-[1,3,2]dioxaborinane

18 The use according to any one of claims 7-16, wherein R^3 is characterized in pK_a of the compound R^3-$B(OH)_2$ being between 2 0 and 11 5, between 3 0 and 10 5, between 4 0 and 9 5, between 5 0 and 8 5, preferably between 5 5 to 8 0, and most preferable between 6 0 to 7 5

19 The use according to any one of claims 1-18, wherein said boronic acid, or an est r thereof or a prodrug thereof has a molar weight of no greater than 1000 D

20 The use according to any one of claims 1-19, wherein the molar weight of said boronic acid, an ester thereof or a prodrug thereof is less than 750 D, preferably less than 500 D, more preferable less than 350 D, more preferable less than 300 D, more preferable less than 250 D and even more preferable less than 200 D

21 The use according to any one of claims 1-20, wherein said boronic acid, an ester thereof or a prodrug thereof has an IC_{50} value as determined by the assay 3190 2 or 3180 1 disclosed herein of less than 50 μM, preferably less than 5 μM, more preferable less than 500 nM and even more preferable less than 100 nM

22 The use according to any one of claims 1-21, wherein said boronic acid, an ester thereof or a prodrug thereof has a solubility in water at 25 °C and pH 2 0 of at least 0 5 mg/L, preferably at least 2 5 mg/L, more preferable at least 20 mg/L, even more preferable at least 200 mg/L and most preferable at least 2 g/L

23 The use according to any one of claims 1-22, wherein administration of said boronic acid, an ester thereof or a prodrug thereof is by the oral, nasal, transdermal, pulmonal, or parenteral route

24 A pharmaceutical composition for the use according to any one of claims 1-2, wherein said pharmaceutical composition comprises, as an active ingredient, a boronic acid, an ester thereof, a prodrug thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, together with a pharmaceutically acceptable carrier or diluent

25 A pharmaceutical composition for the use according to any one of claims 1-2, wherein said pharmaceutical composition comprises, as an active ingredient, a boronic acid, an ester thereof or a prodrug thereof as defined in any one of claims 3-22, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent

26 The pharmaceutical composition according to any one of claims 24-25 in unit dosage form, comprising from about 0 05 mg to about 2000 mg, preferably from about 0 1 to about

500 mg of the boronic acid, an ester thereof, a prodrug thereof or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof as defined in any one of claims 3-22

27 The pharmaceutical composition according to any one of claims 24-26 for oral, nasal, transdermal, pulmonal or parenteral administration

28 A method of treating any disorder where it is desirable to inhibit the lipolytic activity of hormone-sensitive lipase against triacylglycerols, diacylglycerols, cholesterol acyl esters or steroid acyl esters, wherein said method comprises the use according to any one of claims 1-23

29 A method of treating any disorder where it is desirable to modulate the plasma level of free fatty acids or to modulate the handling, storage and oxidation of intracellular fatty acid and cholesterol, wherein said method comprises the use according to any one of claims 1-23

30 The method according to any one of claims 28-29, wherein said disorder is selected from the group consisting of insulin resistance, diabetes type 1, diabetes type 2, metabolic syndrome X, impaired glucose tolerance, hyperglycemia, dyslipidemia, obesity, abnormalities of lipoprotein metabolism and any combination thereof

31 A method of treating a patient suffering from insulin resistance, diabetes type 1, diabetes type 2, metabolic syndrome X, impaired glucose tolerance, hyperglycemia, dyslipidemia, hyperlipoproteinemia, hypertriglyceridemia, hyperlipidemia, hypercholesterolemia, or other abnormalities of lipoprotein metabolism, said method comprising administering to the patient a pharmaceutically effective amount of a boronic acid, an ester thereof, a prodrug thereof or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof

32 The method according to claim 31, wherein said boronic acid or an ester thereof, or a prodrug thereof is a compound according to any one of claims 3-22

33 The method according to any one of claims 28-32, wherein the patient is treated with said boronic acid, an ester thereof, a prodrug thereof or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof for at least about 1 week, for at

least about 2 weeks, for at least about 4 weeks, for at least about 2 months or for at least about 4 months

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ABSTRACT

Use of compounds to inhibit hormone-sensitive lipase, the use of these compounds as pharmaceutical compositions, pharmaceutical compositions comprising the compounds, method of treatment employing these compounds and compositions, and novel compounds The present compounds are inhibitors of hormone-sensitve lipase and may be useful in the treatment and/or prevention of a range of medical disorders where a decreased activity of hormone-sensitive lipase is desirable